Poster number: 4.2

Untargeted proteomics in the GENFI cohort: the discovery of novel biomarkers for genetic frontotemporal dementia.

Aitana Sogorb-Esteve[1,2*], Sophia Weiner[3*], Joel Simrén[3*], Mathias Sauer[3], Imogen J Swift[1,2], Carolin Heller[1,2], Kathryn Knowles[1,2], GENFI consortium, Kaj Blennow[3], Henrik Zetterberg[1,3], Johan Gobom[3*], and Jonathan D Rohrer[1,2*]

1. UK Dementia Research Institute at University College London, London, United Kingdom
2. Dementia Research Centre, University College London, London, United Kingdom
3. Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, University of Gothenburg, Mölndal, Sweden.

OBJECTIVES

In this study we explored the proteomic signatures of each genetic form of frontotemporal dementia (FTD) using an unbiased approach for the discovery of novel fluid biomarkers.

COHORT AND METHODS

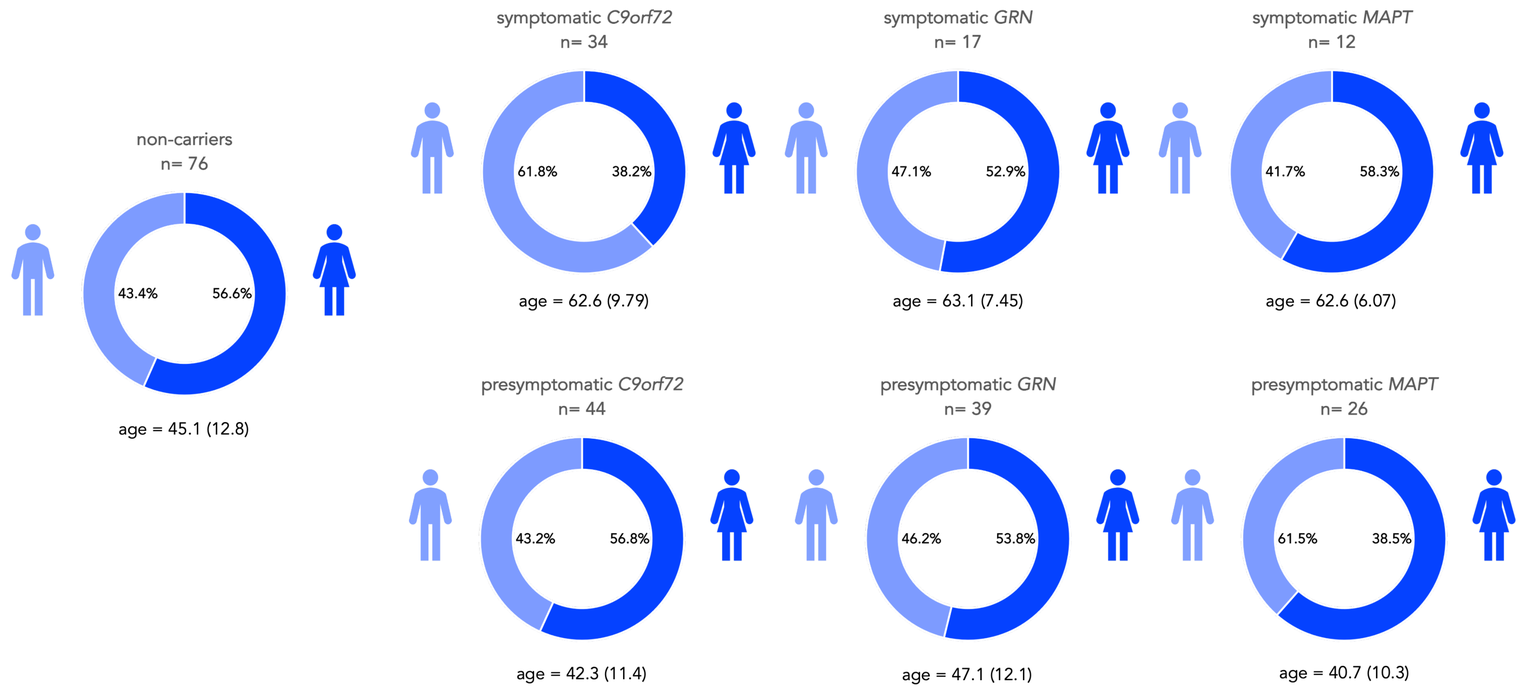

Figure 1. Participant demographics. Age indicated as mean(sd).

A total of 248 cerebrospinal fluid (CSF) samples from the GENetic FTD Initiative including 109 presymptomatic and 63 symptomatic mutation carriers as well as 76 mutation-negative controls were analysed for this study. For the proteomic analysis we used liquid chromatography coupled to mass spectrometry (LC-MS), employing the tandem mass tag (TMT) technique for multiplex quantification.

RESULTS

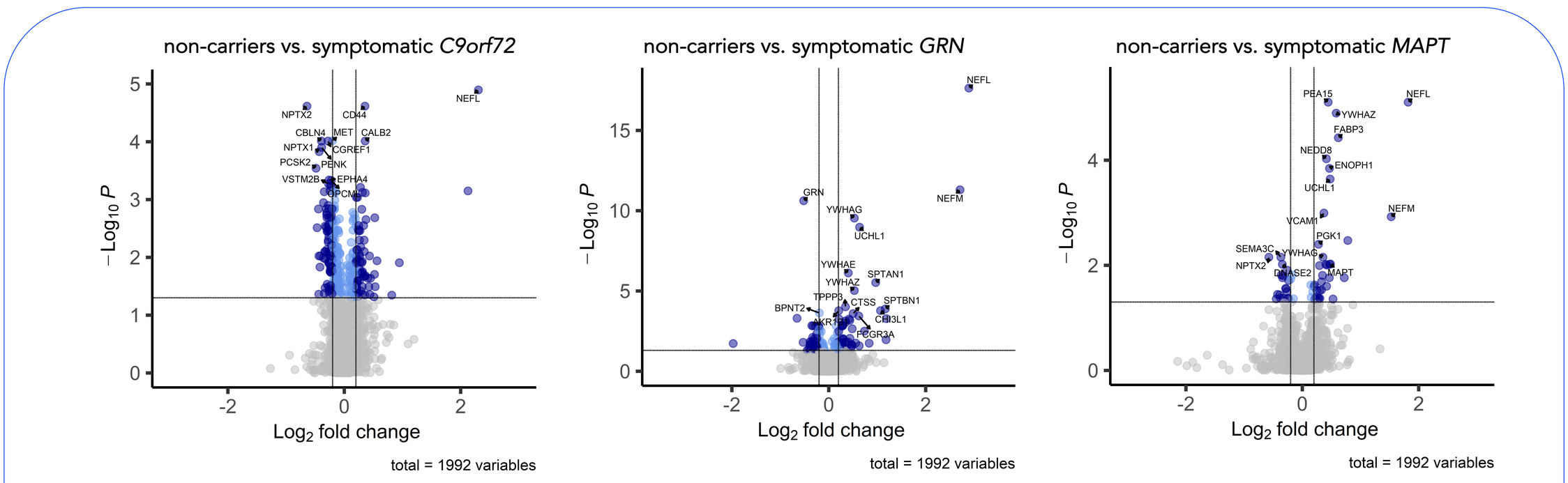

Figure 2. Volcano plot for symptomatic mutation carriers. Volcano plots generated from ANCOVA analysis with Benjamini-Hochberg correction. Names are shown for the top 15 hits. Only symptomatic groups vs non-carrier comparisons shown. non-significant, significant p-value, significant p-value and $\log_2$ fold change.

Using ANCOVA analysis with Benjamini-Hochberg correction for multiple comparisons we identified specific proteomic signatures for each of the genetic forms. Our results are validated by the presence of upregulation in neurofilament light chain (NEFL) and ubiquitin carboxyl-terminal hydrolase isozyme 1 (UCHL1) as well as downregulation of progranulin (GRN) in the *GRN* mutation carriers. We also found interesting new candidates like CD44, which are altered in the three genetic forms.

We then identified via LASSO algorithm 26 proteins in total that best explain the variance among non-carriers, symptomatic *C9orf72*, *GRN* and *MAPT* mutation carriers (Table 1).

Finally, we explored the overlap of significantly differently regulated proteins between the genetic groups, and we found that only 14 proteins overlapped in the three groups and there is a larger overlap related to the underlying pathology, separating *C9orf72* and *GRN* (TDP-43 pathology) from *MAPT* (Figure 3).

SLC9A3R1	Na(+) exchange regulatory cofactor NHE-RF1
TNFSF12	Tumor necrosis factor ligand superfamily member 12
NPTXR	Neuronal pentraxin receptor
PENK	Proenkephalin-A
IGLV2-11	Immunoglobulin lambda variable 2-11
MMP3	Stromelysin-1
SOD3	Extracellular superoxide dismutase [Cu-Zn]
FCGR3A	Low affinity immunoglobulin gamma Fc region receptor III-A
UCHL1	Ubiquitin carboxyl-terminal hydrolase isozyme L1
CD44	CD44 antigen
CEL	Bile salt-activated lipase
CALB2	Calretinin
CTSS	Cathepsin S
GRN	Progranulin
CRIP2	Cysteine-rich protein 2
YWHAG	14-3-3 protein gamma
YWHAZ	14-3-3 protein zeta/delta
FKBP4	Peptidyl-prolyl cis-trans isomerase FKBP4
SPTAN1	Spectrin alpha chain, non-erythrocytic 1
GASK1B	Golgi-associated kinase 1B
GLDN	Gliomedin
PLBD2	Putative phospholipase B-like 2
NRGN	Neurogranin
ACO2	Aconitate hydrase, mitochondrial
ANGPTL2	Angiopoietin-related protein 2
UFC1	Ubiquitin-fold modifier-conjugating enzyme 1

Table 1. Proteins identified via LASSO.

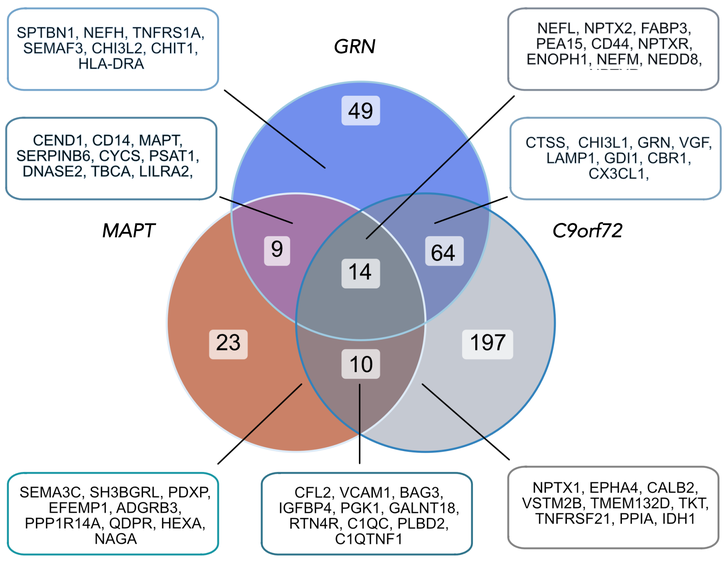

Figure 3. Venn diagram of overlapping differently regulated proteins in the symptomatic groups.

CONCLUSION

As the first study of untargeted proteomics in the GENFI cohort, this work will provide valuable insight into novel fluid biomarker candidates that may be helpful to track disease progression. The results have been validated by correlation with previous studies and network analyses are now being performed for a better understanding of the biological processes implicated in each genetic form.

Acknowledgements: We thank the research participants for their contribution to the study. This work was supported by Race Against Dementia.

a.sogorb-esteve@ucl.ac.uk @aitanasogorb